

December 4, 1997

page 2

At page 21, line 16, replace "inveniton" with --invention--.

At page 25, line 16, replace "andd" with --and--.

At page 25, line 17, replace "resuspened" with --resuspended--.

NE At page 25, line 24, replace "polyethyleneimine" with --polyethylene--.

At page 25, line 26, replace the second occurrence of "the" with --The--.

At page 26, line 8, replace "inveniton" with --invention--.

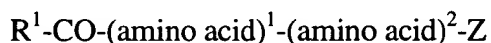
## IN THE CLAIMS

Cancel claims 4 and 9.

Amend claim 1 to read:

1 (amended). A reagent for preparing a scintigraphic imaging agent [for imaging a site within a mammalian body], comprising a specific binding compound [that is] having a molecular weight of less than 10,000 daltons [in molecular weight] , the compound being covalently linked to a radiolabel complexing moiety having a formula selected from the group consisting of:

I.



wherein (amino acid)<sup>1</sup> and (amino acid)<sup>2</sup> are each independently any primary  $\alpha$ - or  $\beta$ -amino acid that does not [comprise] contain a thiol group;

Z is [a thiol-containing moiety that is] selected from the group consisting of cysteine, homocysteine, isocysteine, penicillamine, 2-mercaptoethylamine [or] and 3-mercaptopyrrolamine;

R<sup>1</sup> is lower (C<sup>1</sup>-C<sup>4</sup>) alkyl or a covalent linkage to the [specific binding] compound;

wherein

when Z is cysteine, homocysteine, isocysteine or penicillamine, [the] Z comprises a carbonyl group [of said moiety is] covalently linked to a hydroxyl group, a NR<sup>3</sup>R<sup>4</sup> group wherein R<sup>3</sup> and R<sup>4</sup> are each independently H or lower (C<sup>1</sup>-C<sup>4</sup>) alkyl, an amino acid, or a peptide comprising 2 to 10 amino

JFL  
10-31-2002

Revised

acids, [and wherein  $R^3$  and  $R^4$  are each independently H or lower ( $C^1-C^4$ ) alkyl];

[or] and

## II.

$Y-(\text{amino acid})^2-(\text{amino acid})^1-NHR^2$

wherein Y is [a thiol-containing moiety that is] selected from the group consisting of cysteine, homocysteine, isocysteine, penicillamine, 2-mercaptoacetate [or] and 3-mercaptopropionate;

(amino acid)<sup>1</sup> and (amino acid)<sup>2</sup> are each independently any primary  $\alpha$ - or  $\beta$ -amino acid that does not [comprise] contain a thiol group;

$R^2$  is selected from the group consisting of H, a [or] lower ( $C^1-C^4$ ) alkyl, and [or] a covalent linkage to the [specific binding] compound;

wherein when Y is cysteine, homocysteine, isocysteine or penicillamine, [the] Y comprises an amino group [of said moiety is] covalently linked to -H, an amino acid, or a peptide comprising 2 to 10 amino acids; and

wherein the [radiolabel complexing] moiety is [covalently] linked to the [specific binding] compound through  $R^1$ ,  $R^2$ , a sidechain group of [the sidechain of] (amino acid)<sup>1</sup>, [or] a sidechain group of (amino acid)<sup>2</sup>, [or the] an amino group of cysteine, homocysteine, isocysteine, or penicillamine, or a carboxyl group of cysteine, homocysteine, isocysteine or penicillamine.

Amend claim 2 to read:

2 (amended). The reagent of Claim 1 wherein the radiolabel complexing moiety is selected [fromn] from the group consisting of [moieties having the formula]:

$-(\text{amino acid})^1-(\text{amino acid})^2-(\text{amino thiol}),$

and  $(\text{mercaptocarboxylic acid})-(\text{amino acid})^1-(\text{amino acid})^2-$ ,

wherein (amino acid)<sup>1</sup> and (amino acid)<sup>2</sup> are each independently any primary  $\alpha$ - or  $\beta$ -amino acid;

(amino thiol) is selected [fromn] from the group consisting of cysteine, isocysteine, homocysteine, [penicilamine] penicillamine, 2-mercaptoethylamine, and 3-mercaptopropylamine; and

(mercaptocarboxylic acid) is selected [fromn] from the group consisting of cysteine, isocysteine, homocysteine, [penicilamine] penicillamine, 2-mercaptoacetic acid, and [3-mercaptopropionic] 3-mercaptopropionic acid.

*B. Condit*

Amend claim 3 to read:

3 (amended). The reagent of Claim 2 wherein the radiolabel complexing moiety is selected from the group consisting of [moieties having the formula] -Gly-Gly-Cys- [or] and Cys-Gly-Gly-.

Amend claim 5 to read:

5 (amended). A reagent according to Claim 1 wherein the [specific binding] compound is a [a specific binding] peptide comprising 4 to 100 amino acids.

*B. Condit*

Amend claim 6 to read:

6 (amended). The reagent of Claim [1] 5 wherein the [specific binding] peptide and the [radiolabel binding] moiety are [covalently] linked through one or more amino acids.

Amend claim 10 to read:

10 (amended). The reagent of Claim [9] 24 wherein the polyvalent linking moiety is [*bis*-succinimidylmethylether] selected from the group consisting of *bis*-succinimidylmethylether, 4-(2,2-dimethylacetyl)benzoic acid, *tris*(succinimidylethyl) amine, 4-(O-CH<sub>2</sub>CO-Gly-Gly-Cys.amide)acetophenone, *bis*-succinimidohexane, *tris*(2-chloroacetamidoethyl)amine, [and] 1,2-*bis*-(2-(chloroacetamido)ethoxy)ethane, [or a derivative thereof] a derivative of *bis*-succinimidylmethylether, a derivative of 4-(2,2-dimethylacetyl)benzoic acid, a derivative of *tris*(succinimidylethyl) amine, a derivative of 4-

*B. Condit*

*B3*  
(O-CH<sub>2</sub>CO-Gly-Gly-Cys.amide)acetophenone, a derivative of bis-succinimidohexane, a derivative of tris(2-chloroacetamidoethyl)amine, and a derivative of 1,2-bis-[2-(chloroacetamido)ethoxy]ethane.

Amend claim 18 to read:

18 (amended). A composition of matter having a formula selected from the group consisting of:

*B4*  
cyclo(N-methyl)FYW<sub>D</sub>KV.Hcy.(CH<sub>2</sub>CO.GGC.amide)<sub>1</sub>  
cyclo(N-methyl)FYW<sub>D</sub>KV.Hcy.(CH<sub>2</sub>CO.GGCK.amide)<sub>1</sub>  
cyclo(N-methyl)FYW<sub>D</sub>KV.Hcy.(CH<sub>2</sub>CO.GGCR.amide)<sub>1</sub>  
cyclo(N-methyl)FYW<sub>D</sub>KV.Hcy.(CH<sub>2</sub>CO.GGCRD.amide)<sub>1</sub>  
cyclo(N-methyl)FYW<sub>D</sub>KV.Hcy.(CH<sub>2</sub>CO.GGCRK.amide)<sub>1</sub>  
cyclo(N-methyl)FYW<sub>D</sub>KV.Hcy.(CH<sub>2</sub>CO.GGCRR.amide)<sub>1</sub>  
cyclo(N-methyl)FYW<sub>D</sub>KV.Hcy.(CH<sub>2</sub>CO.GGCKK.amide)<sub>1</sub>  
cyclo(N-methyl)FYW<sub>D</sub>KV.Hcy.(CH<sub>2</sub>CO.GGCKKK.amide)<sub>1</sub>  
cyclo(N-methyl)FYW<sub>D</sub>KV.Hcy.(CH<sub>2</sub>CO.GGC.Orn.amide)<sub>1</sub>  
cyclo(N-methyl)FYW<sub>D</sub>KV.Hcy.(CH<sub>2</sub>CO.GGCKDK.amide)<sub>1</sub>  
cyclo(N-methyl)FYW<sub>D</sub>KV.Hcy.(CH<sub>2</sub>CO.GGC.Orn.D.Orn.amide)<sub>1</sub>  
cyclo(N-methyl)FYW<sub>D</sub>KV.Hcy.(CH<sub>2</sub>CO.GGC.Orn.D.amide)<sub>1</sub>  
cyclo(N-methyl)FYW<sub>D</sub>KV.Hcy.(CH<sub>2</sub>CO.KKC.amide)<sub>1</sub>  
cyclo(N-methyl)FYW<sub>D</sub>KV.Hcy.(CH<sub>2</sub>CO.KRC.amide)<sub>1</sub>  
cyclo(N-methyl)FYW<sub>D</sub>KV.Hcy.(CH<sub>2</sub>CO.RRC.amide)<sub>1</sub>  
cyclo(N-methyl)FYW<sub>D</sub>KV.Hcy.(CH<sub>2</sub>CO.KKCK.amide)<sub>1</sub>  
cyclo(N-methyl)FYW<sub>D</sub>KV.Hcy.(CH<sub>2</sub>CO.GRCK.amide)<sub>1</sub>  
cyclo(N-methyl)FYW<sub>D</sub>KV.Hcy.(CH<sub>2</sub>CO.GKCR.amide)<sub>1</sub>  
CH<sub>2</sub>CO.Y<sub>D</sub>.Apc.GDCGGC<sub>Ac</sub>GC<sub>Ac</sub>GGC.amide<sub>1</sub>  
CH<sub>2</sub>CO.Y<sub>D</sub>.Apc.GDCGGC<sub>Ac</sub>GC<sub>Ac</sub>GGCG.amide<sub>1</sub>  
CH<sub>2</sub>CO.Y<sub>D</sub>.Apc.GDCGGSSGGCG.amide<sub>1</sub>  
CH<sub>2</sub>CO.Y<sub>D</sub>.Apc.GDCGGCG.amide<sub>1</sub>  
GRGDGGC<sub>1</sub>  
GLFCGC.amide<sub>1</sub>  
GRGDGGGGC<sub>1</sub>  
F<sub>D</sub>FYW<sub>D</sub>KTFTGGC.amide<sub>1</sub>  
acetyl.CGGY.(CH<sub>2</sub>)<sub>4</sub>-piperidine<sub>1</sub>  
[or] and  
β-glucan-(=NNHCO.(CH<sub>2</sub>)<sub>3</sub>CO.)GGC.amide

Amend claim 19 to read:

19 (amended). The reagent of Claim [1] 5 wherein the [specific binding] peptide [is comprised of] comprises a linear peptide or a cyclic [peptides] peptide.

*B4 cancelled.*  
Amend claim 20 to read:

20 (amended). The reagent of Claim 1 wherein the [imaged site within a mammalian body is] compound binds to a thrombus site.

Amend claim 21 to read:

21 (amended). The reagent of Claim 1 wherein the [imaged site within a mammalian body is] compound binds to a site of an infection.

Please add new claims 24 through 33 as set forth below.

24. A multimer comprising a polyvalent linker covalently linked to at least two copies of the reagent of claim 1, said multimer having a molecular weight less than about 20,000 daltons.

*B5 cancelled.*  
25. A peptide reagent comprising  
a first peptide that localizes at a target site in a mammalian body; and  
a second peptide that binds technetium-99m and has a formula selected from the group consisting of Gly-Gly-Cys, Gly-Gly-Pen, Gly-Gly-Gly-Cys, Gly-Gly-Gly-Pen, and D-stereoisomers thereof,  
wherein the first peptide is covalently linked to the second peptide.

26. The reagent of claim 25, further comprising technetium-99m complexed with the second peptide.

27. A method of labeling a peptide with technetium-99m comprising the steps of

a) combining:

a solution containing a peptide reagent comprising

a first peptide that localizes at a target site in a mammalian body; and

a second peptide that binds technetium-99m and has a formula selected from the group consisting of Gly-Gly-Cys, Gly-Gly-Pen, Gly-Gly-Gly-Cys, Gly-Gly-Gly-Pen, and D-stereoisomers thereof, wherein the first peptide is covalently linked to the second peptide,

and technetium-99m for a time and at a temperature sufficient to allow a complex to form between the second peptide and the technetium-99m; and

b) recovering radiolabeled peptide.

28. The method of claim 27, wherein the solution further comprises stannous ions, in an amount sufficient to label the reagent with technetium-99m.

29. The method of claim 28, wherein the technetium-99m is in the form of pertechnetate.

B5  
Beamed

30. A method of radiolabeling a peptide reagent with technetium-99m, wherein the reagent comprises:

a first peptide that localizes at a target site in a mammalian body; and

a second peptide capable of binding technetium-99m and has a formula selected from the group consisting of Gly-Gly-Cys, Gly-Gly-Pen, Gly-Gly-Gly-Cys, Gly-Gly-Gly-Pen, and D-stereoisomers thereof, the first peptide being covalently linked to the second peptide,

comprising the steps of:

- PS Beantel
- a) combining said reagent with an amount of stannous ion sufficient to reduce said technetium-99m in an aqueous medium to form a solution;
  - b) reacting the solution with the technetium-99m; and
  - c) recovering the radiolabeled reagent.

31. The method of claim 30, wherein the reagent and the stannous ion are provided in lyophilized form.

32. A method for visualizing a site within a mammalian body comprising the steps of:

- a) administering to the body a peptide reagent comprising  
a first peptide that localizes at a target site in a mammalian body; and

a second peptide complexed with technetium-99m and has a formula selected from the group consisting of Gly-Gly-Cys, Gly-Gly-Pen, Gly-Gly-Gly-Cys, Gly-